European Food Safety Authority

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TECHNICAL REPORT

Outcome of the public consultation on the draft guidance on statistical reporting [1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The EFSA has undertaken a public consultation on the draft guidance on statistical reporting. The draft guidance was prepared by a dedicated working group. The task of the working group is to improve quality, openness and transparency of EFSA's work and information/analyses received by EFSA (including dossiers). It is not intended to provide guidance on which statistical methodology should be applied and how statistical analysis should be performed. A template was proposed, that covers in the broadest possible way, the reporting of relevant aspects of a statistical analysis including: objectives, sources of information (data), study design, data quality, analysis methods, results and interpretation. The guidance and template serve to harmonise and standardise statistical reporting to allow for reproducibility of results and to facilitate independent peer review. The draft version presented the intermediate results after the first half of the project. The public consultation was launched on 28 May 2014 and closed on 23 July2014. The comments provided insight into several potential difficulties in the text of the draft guidance and thus, enhanced the quality of the document. The relevant comments were taken into account and the guidance document was revised accordingly. The Working Group on guidance on statistical reporting acknowledges the usefulness and quality of the comments received and would like to thank all commentators for their interest and input to its current and future work. EFSA has committed to publish a technical report on the outcome of the public consultation on the guidance and presents hereafter the responses of the working group to the comments it received.

KEY WORDS

statistical reporting, study design, sampling, guidance, statistics

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BACKGROUND AS PROVIDED BY EFSA

EFSA's mission is to support policy makers in their activity by providing and analysing scientific evidence. There are differences in the requirements for statistical reporting in regulatory and research setting. In a research setting, the audience is primarily comprised of peers with scientific expertise in the topic, whereas in a regulatory setting the primary expertise of the audience may be in other areas of science, or outside science (e.g. in policy, economics, law, etc.). Furthermore, in a research setting the focus is on advancing knowledge, including the development and testing of hypotheses, whereas in a regulatory setting the focus is on making decisions between alternative policies or regulatory options. These differences have implications for statistical reporting. In a research setting, it is common to report in detail the methods and assumptions of an analysis, and discuss their validity: the audience may then use their own expertise to interpret critically the implications of the results and any associated uncertainties. In a regulatory setting, detailed description is also important for transparency and peer review, but the regulatory audience will often lack the expertise to interpret for themselves the impact of assumptions and uncertainties on the conclusions. Therefore, in a regulatory setting, it is essential not only to report assumptions and the degree to which they are valid, but also to evaluate and express the impact of this on the interpretation of the results. EFSA work includes evaluations of submissions from external organisations in relation to regulated products and techniques. In this context, the reports delivered as supporting documents to EFSA frequently lack key information. As a consequence there is a need to request clarifications, thus increasing the time and the effort needed for the assessment. The availability of clear and detailed recommendations on the reporting should help to shorten the process and minimise disputes.

The risk assessment process often requires quantitative evaluation of scientific studies from different sources (e.g. dossiers, journal publications, technical reports). The reporting of statistical methodology (including design), analysis and results varies considerably. Lack of relevant information can lead to delays in the review process whilst additional information is sought from the originating source. For the statistics were consistently reported in a harmonised and standardised way then this would benefit of both EFSA and its stakeholders, this guidance aims for harmonisation and standardisation through the provision of guidelines on peer review and reproducibility. It is designed to improve the quality, openness and transparency of the work of stakeholders reporting to EFSA and of EFSA's own work in this area. It is aimed at EFSA panels, Scientific Committee, working groups, units and stakeholders.

TERMS OF REFERENCE AS PROVIDED BY EFSA

In view of the above, guidelines should be developed to best guide EFSA panels, Scientific Committee, working groups, units and stakeholders on how to clearly and concisely report statistical methodology (including design and conduct), analyses and results (i.e. "explain to the reader what was done"). The issue of what methodologies should be used for the design, conduct and analysis are outside the scope of this mandate.

The Guidance should be practical and applicable to the different relevant food and feed safety fields, within EFSA's remit including Animal Health and Welfare and Plant Health. In particular, the EFSA Guidance should include:

- How to ensure objective and accurate reporting of statistics
- How to document and present the design, methodology, analysis and results to allow independent peer review
- A glossary of relevant terms.

A draft version of the Guidance should be made available for the Scientific Committee and for public consultation, to ensure all relevant information is taken into account with respect to the reliability and consistency of the methods described in the final document.

For the development of this EFSA Guidance, the SAS Unit should establish a working group of EFSA scientific staff and external experts.

CONSIDERATION OF RECEIVED COMMENTS

1. INTRODUCTION

During the public consultation launched on the draft guidance on guidance on statistical reporting (see Appendix A), the European Food Safety Authority (EFSA) received comments from sixteen interested parties including two national competent authorities and two universities. All the comments received are listed in the Appendix B. Additional internal comments were also received and taken into account.

2. SCREENING AND EVALUATION OF COMMENTS RECEIVED

All comments were scrutinised and assessed by the Working Group over four meetings from 2nd October 2014 to 22nd October 2014. The comments were compiled in a table with reference to the contributor and to the section of the draft scientific opinion to which the comment referred. The response of the working group to each comment is available in the last column of the table (see Appendix B). Apart from comments regarding improvement of specific details of the guidance, the Working Group also received some comments on the structure and readability of the Guidance.

3. INCORPORATION OF THE COMMENTS IN THE GUIDANCE DOCUMENT

The Working Group reviewed all the comments and discussed how to address them in the guidance. The comments provided insight into several potential difficulties in the text of the draft guidance and thus, contributed to an enhancement of the quality of the document. The relevant comments were taken into account and the guidance document was revised accordingly.

A final draft of this technical report was approved by the Working Group on 28th October 2014 and sent to EFSA's Scientific Committee for endorsement. The Technical Report and the final Guidance Document will be published together on 2nd December 2014.

CONCLUSIONS

When revising the draft Statistical Reporting Guidance, all comments received through the public consultation were scrutinised and considered by the Working Group on statistical reporting.

The EFSA working group acknowledges the usefulness and quality of the comments received and would like to thank all commentators for their interest and input to its current and future work.

APPENDICES

Appendix A. THE TEXT OF THE PUBLIC CONSULTATION FROM THE EFSA WEBSITE

Explanatory text to advertise the public consultation (EFSA web text, communication to the Advisory Forum, national Focal Points, stakeholders, Stakeholder Consultative Platform, and/or other relevant networks identified)

EFSA's Assessment and Methodological Support Unit has launched an open consultation on the draft of its Guidance on Statistical Reporting. The guidance aims to assist harmonisation and standardisation in the reporting of statistical analysis.

The risk assessment process often requires quantitative evaluation of scientific studies from different sources, such as dossiers, journal publications, and technical reports. The reporting of statistical methodology, analyses and results varies considerably. Lack of relevant information can lead to delays in the review process whilst additional information is sought from the originating source. If statistics were reported in a harmonised and standardised way this would benefit EFSA and its stakeholders. This approach would also be more open and transparent.

The document should guide EFSA's Scientific Committee, its Scientific Panels, working groups, units and stakeholders on how to report statistical methodology (including design and conduct), analyses and results (i.e. "explain to the reader what was done") to allow independent peer review and reproducibility.

In line with EFSA's policy on openness and transparency and in order for the Authority to receive comments from the scientific community and stakeholders, EFSA has launched a public consultation on the draft document.

Interested parties are invited to submit written comments by 23 July 2014.

Please use exclusively the electronic template provided with the documents to submit comments and refer to the line and page numbers. Comments submitted by email or by post cannot be taken into account and a submission will not be considered if it is:

- Submitted after the deadline set out in the call
- Presented in any form other than what is provided for in the instructions and template
- Not related to the contents of the document
- Contains complaints against institutions, personal accusations, irrelevant or offensive statements or material
- Is related to policy or risk management aspects, which is out of the scope of EFSA's activity.

EFSA will assess all comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA working group and taken into consideration if found to be relevant.

All comments submitted will be published. Comments submitted by individuals in a personal capacity will be presented anonymously. Comments submitted formally on behalf of an organisation will appear with the name of the organisation.

Appendix B. COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION ON THE DRAFT GUIDANCE ON STATISTICAL REPORTING

The section and line numbers refer to the version published for consultation: http://www.efsa.europa.eu/en/consultationsclosed/call/130813.pdf

No	Contributor	Section	Comments received	EFSA answers
1	DSM Nutritional Products (CHE)	Abstract	Line 13-14 "... The guidance and template serve to harmonise and standardise statistical reporting to allow for reproducibility of results and to facilitate independent peer review." We absolutely support EFSA's aim of harmonization, transparency and reproducibility. The guidance should also address the way EFSA will evaluate reports generated before publication of the guidance document which followed generally accepted scientific rules at the time of preparation. This relates to the question to what extent existing study reports can still be used in the future. Research is usually a long-term effort which requires considerable investment over many years. Will EFSA take into account already existing evidence if the reporting is scientifically sound and fulfils the most important points in the guidance? Is EFSA considering a transition period for documents written before the guidance was published?	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
2	OCS (NLD)	Abstract	Line 13 "… harmonise and standardize statistical reporting to allow for reproducibility of results" Why would standardization allow reproducibility? A non-standardized but complete and transparent description would serve this. Standardization could say more about efficiency and enhance comparability of results from various sources. Suggestion to rephrase.	This comment has been taken into account in revising the Abstract.

No	Contributor	Section	Comments received	EFSA answers
3	Nestlé (CHE)	Abstract	Chapter/Section Abstract Line numbers 8-14 Nestlé Comments Nestlé finds that this guidance is a good forward looking document that will help standardization and transparency. Standardization is needed for statistical reporting of clinical trials used in dossiers submitted to EFSA and Nestlé welcomes this initiative. However Nestlé would like to understand how this guidance will influence dossier writing, since the information and all data required in this guidance are not always available to the applicant. This guidance should not add restriction on how to prepare dossiers for the substantiation of health claims. Typically Nestlé agrees that this guidance suits the reporting of new studies and should be followed for pivotal and proprietary clinical studies submitted in dossier for health claim substantiation; however adherence to this guidance may not be feasible for all already existing historical data and published studies. Indeed for different reasons it may not be possible to go back to the author of historical studies and the related publications may not have all required information: Therefore the application of this guidance should be based on practical, reasonable and proportional grounds. Nestlé would like that harmonization is sought between EFSA and other authorities where dossiers are submitted.	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance". EFSA contacted other European Union agencies for their feedback and the public consultation was open to all other authorities for their comments.
4	Association of the Self-Medication Industry	Abstract	General comments Companies have produced internal report templates for the statistical reporting issues. The companies note that their internal reports content is considered to be	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability

No	Contributor	Section	Comments received	EFSA answers
	(AESGP) (BEL)		aligned with EFSA's proposed guidance document. However, these internal report templates, which are also used for submissions to other regulatory authorities, are not structured as per EFSA guidance. The interpretation is that the EFSA document is a guidance document outlining the expected content rather than a mandate for report structure. EFSA is kindly requested to confirm this interpretation. In particular (relating to the above comment), there are mentions of required content within the reporting which is considered to be adequately covered within the companies' internal protocols produced prior to study conduct. Since relevant protocols would be included within any submission to EFSA, it would be considered necessary to re-state within the report text unless either salient to report text understanding or if a change to the plan has occurred. EFSA is kindly requested to confirm this interpretation.	of This Guidance".
5	Technical University of Denmark (DNK)	Abstract	*Same comment repeated in Sections:* • *Summary* • *Background as provided by EFSA* • *Applicability of Statistical Reporting Guidance* • *Other guidance documents on related topics* • *Reporting Uncertainty* The term 'risk analysis' is mentioned many times in the document. While it is a suitable motivator to point to the applications of statistics within risk analysis, it is also mentioned in the guidance paper (lines 151 and onwards) that "…guidelines should be developed to best guide EFSA panels, Scientific Committee,	The individual detailed comments are addressed below.

No	Contributor	Section	Comments received	EFSA answers
			Working groups, units and stakeholders on how to clearly and concisely report statistical methodology (including design and conduct), analyses and results (i.e. 'explain to the reader what was done').This formulation also appears in the summary (lines 31-33). Thus, it does not appear from the above that risk analysis is part of the scope of the document. Yet, in the section 'Applicability of Statistical Reporting Guidance' (lines 179-185), the objective of the document is formulated as '…to provide guidance on how to report statistical work in order to allow the evaluation of the quality and validity for any analysis for appropriate use in EFSA's risk assessment process, including dossier reviews…'. It seems an unnecessary restriction only to relate to the risk assessment process, and it appears to be in contrast to the statement in line 169 that the guidance is '….aimed at covering all areas of EFSA's remit….', and indeed the title of the document. While the true intentions of EFSA in this case are not known, it is suspected that the restriction to risk analysis is unintended. If so, the focus will be confusing for analysts looking for guidance for other application areas. Suggestion: It is suggested that the term 'risk analysis' is removed from the guidance, except for where it is listed as motivator or application area for statistical reporting. In particular, the following points are suggested: • The objective of the document in lines 180-183 is reformulated without the term risk assessment, to comply with the aim in line 169	

No	Contributor	Section	Comments received	EFSA answers
			• The quote from EFSA(2009) in lines 206-221 is either removed, or the reason for quoting it is subsequently explained in terms of statistical reporting • Section 10.2 should be formulated with focus on statistical reporting rather than risk analysis • The summary, the abstract and the section on "Background as provided by EFSA" should be rewritten according to the above, so that risk analysis will appear as a motivator and/or application area, but not as the subject of the guidance. The reason for these suggested changes is the confusion that may arise when analysts and/or report writers from other application areas look for guidance on statistical reporting.	
6	Global Alliance for Probiotics (GAP) (BEL)	Abstract	It is felt that the publication of this guidance is not the most opportune under the circumstances in which widely-spread, reliable and well-investigated standardised statistical methodologies are already available. We would ask that EFSA harmonise its guidance with pre-existing standards, and that EFSA holds further discussions with external experts in individual fields when EFSA seeks to establish rules. The guidelines in their present form are overly strict for certain areas.	The applicability of the guidance in given in the "Terms of Reference as Provided by EFSA". This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
7	Food Standards Agency (GBR)	Summary	Overall, it is not clear who this guidance is addressed at. Especially it is not clear how the guidance could be applied in EFSA opinions that potentially cite hundreds of references, many of which use statistical	The applicability of the guidance in given in the "Terms of Reference as Provided by EFSA". This comment has been taken into account in revising

No	Contributor	Section	Comments received	EFSA answers
			approaches that might not be well described	Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
8	Lallemand Health Solutions (CAN)	Summary	Specific Comments Lines 6, 25, 141, etc The term "risk assessment" is used repeatedly throughout the guidance document as the process for which EFSA wishes adequate statistical reporting but, as is indicated in lines 170 - 171, the areas that the guidance is meant to cover is larger than just risk assessment. It also includes safety, efficacy, bio-equivalence, inferiority, and superiority studies. Hence, we recommend that the term risk assessment be replaced throughout the document with a more inclusive term for the projects and studies that the guidance covers.	Your individual detailed comments are addressed below.
9	Lallemand Health Solutions (CAN)	Summary	Comments on the Draft EFSA Guidance on Statistical Reporting We applaud EFSA for providing detailed descriptions of the information that should be provided in any research project that involves statistical analyses and we hope that it becomes the standard approach. General Comments Overall, the document is quite thorough but could be made more succinct. There are several sections that are duplicative and can be consolidated and other sections that require re-organization to maximize their clarity and effectiveness. Finally, the title of the document implies that the emphasis is on reporting statistical methodologies	This comment is covered by the Summary. The Terms of Reference as Provided by EFSA states *"The issue of what methodologies should be used for the design, conduct and analysis are outside the scope of this mandate."* EFSA feels that the title concisely reflects the terms of reference of the mandate and the content of the document.

No	Contributor	Section	Comments received	EFSA answers
			employed in the research but it covers much more than that. Hence, it is unclear whether the guidance is meant to pertain to the entirety of a study (experimental or survey or other) or to only those aspects under the statistical analyses component. In fact, it is a template for the reporting of all aspects of a study or research project including not just the design of the experiment or sampling strategy and the statistical analyses of the data collected but also the rationale for conducting the research, the overall objectives of the study, the data collection effort (e.g. questionnaires or interviews), the inclusion/exclusion criteria, the QA/QC efforts, the data management, the training of individuals in collecting the data, the interpretation of the statistical results, and similar aspects which are not strictly statistical issues. We do not disagree that full guidance should cover all these aspects as well as the statistical reporting since the statistical analyses cannot be fully separated from other components of a well-designed research effort. In fact, the authors explicitly mention (lines 192-194) that the International Conference on Harmonisation (ICH) Guidelines E3 on "Structure and Contents of Clinical Study Reports" was used as a model for the structure of this guidance document. It is also clear that the guidance is meant to cover more than the statistical aspects of a report as is indicated in lines 227-228. Hence, we instead recommend that the title of the guidance be more fully descriptive so as to include these study or experimental aspects that are part of a complete report on a research effort whether	

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			it is an experiment, a survey, a field study, or a meta-analysis and whether it is reported in a dossier, technical report, or a journal. Specific Comments to follow.	
10	HLS (GBR)	Summary	General comment not associated with any specific text: It would take quite a bit of work from both the study director and statistics to pull together all the details contained in their template. Some of the information requested isn't part of what we routinely produce, hence it would be additional work (and cost) to produce all the requirements.	This comment is outside the scope of the mandate.
11	Food Supplements Europe (BEL)	Summary	Food Supplements Europe welcomes this EFSA initiative and takes the possibility to comment on this document. Although we understand this guidance has a wider application, our comments are particularly focusing on its application in relation to submissions for the authorisation of a health claim under Reg 1924/2006. We have two main elements we would want to bring to EFSA's attention: 1. The guidance is very comprehensive and may be a challenge for small and medium sized companies to comply with on top of the already considerable administrative guidance that exist for the different types of applications that require EFSA assessment. In this respect, it is noted that the guidelines, although scientifically sound and covering elaborated statistical reporting, is requesting many elements to be mandatorily reported, which are not even standard within ICH E3 conform clinical trial reports (e.g. 12.5,	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".

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			12.8). The guidelines therefore are likely to considerably raise the hurdle for industry to develop scientifically proven products. Food Supplements Europe would therefore recommend that EFSA could reconsider the guidance to look for simplification wherever possible and to indicate where possible under what conditions certain elements are essential to be included and what elements could be considered as optional. What should definitely be avoided is that study reports are rejected only because of formal incompliance with the guideline (i.e. because a box is not ticked). 2. The guidance is very comprehensive and is likely not to be applicable to research already undertaken and reported. Food Supplements Europe supports the effort to enhance standardization and transparency in reporting of clinical studies. However, this new approach should not lead automatically to research that has already been conducted and published to be discarded because it does not conform all aspects of this guidance. Since studies that have been published have reported their findings in a certain way it may not be possible to have access to all elements of information required or not be feasible to transform the data and results into the format of this guidance. For published data, it is simply not possible to modify study design or reporting of the results. Applicants should be able to continue using non-proprietary published data if these data are of sufficient quality, even if not all elements	

No	Contributor	Section	Comments received	EFSA answers
			of this guidance are applied, as it is not always possible to ask for clarification or extend the information available for historical reason or lack of possibilities from the part of the author. For clarity reasons, we believe that it is essential therefore that the guidance should also address how EFSA will deal with research data and reports that have been developed in compliance with the generally accepted scientific principles and methods that were applicable at the time of undertaking the research, but may now not be in compliance with the new guidance. We would therefore welcome if the guidance document could contain a statement to say that this guidance does not apply to research data that have already been published but that these data will be considered upon their merit, taking into consideration the nature and extent of weaknesses and/or missing information identified. Not being able to consider published research would mean a tremendous loss, not only to substantiate health benefits but also to demonstrate safety. This guidance since it is new, should only apply to guide new research that is intended to support applications (health claims, safety, etc).	
12	Technical University of Denmark (DNK)	Summary	Same as comment 5	Same as comment 5.

No	Contributor	Section	Comments received	EFSA answers
13	GSK (GBR)	Summary	Summary (Line 57) The statement "Descriptive statistics should be presented for all data collected for analysis." is assumed to refer purely to those data for which statistical analyses are planned / performed and not all collected data regardless.	This comment has been taken into account in revising the Summary and Section 9.1.
14	OCS (NLD)	Summary	Line 57 "Descriptive statistics should be presented for all data collected for analysis" is too strict, it should only refer to all data used in the analysis of primary and secondary parameters and maybe exploratory parameters, not necessarily to all data.	This comment has been taken into account in revising the Summary and Section 9.1.
15	EuropaBio (BEL)	Summary	Lines 55–56 The wording "any deviations from any protocol and/or analysis plan must be justified" is confusing. For nutritional composition studies, multiple studies may contribute to the final outcome (one for sample production, one for nutritional analyses, one for statistical analyses), each with its own protocol. Assuming that the requirement here refers just to the statistical analysis, it would be better if this statement said "any deviations from the statistical analysis protocol and/or analysis plan must be justified" so that it is clear that it is referring to deviations in that single protocol and not to deviations in other aspects such as sample production or sample analysis. Lines 55-56. For ag-biotech studies, it is common and accepted for multiple transgenic events to be grown together and/or have their samples analyzed together, even though each will be the subject of a separate submission (EFSA Journal 2010; 8(1):1250). Confidentiality issues will arise if protocols/deviations	This comment has been taken into account in revising the Summary and Section 8.

No	Contributor	Section	Comments received	EFSA answers
			and amendments for these multi-event studies have to be presented.	
16	University of Southampton (GBR)	Summary	Line 52 "approached" should be "approaches".	Corrected.
17	Association of the Self-Medication Industry (AESGP) (BEL)	Summary	Line 57 The statement "Descriptive statistics should be presented for all data collected for analysis." is assumed to refer purely to those data for which statistical analyses are planned / performed and not all collected data regardless. EFSA is kindly requested to confirm this interpretation.	This comment has been taken into account in revising the Summary and Section 9.1.
18	Biofortis (FRA)	Summary	Lines 57-58 Should descriptive statistics be presented for all data collected (whether they are analysed or not) or for all data collected which match with study objectives? We would recommend the second case, as some data may be collected but not yet recorded in the database (only available as raw data for instance), for further exploratory analysis for example.	This comment has been taken into account in revising the Summary and Section 9.1.
19	Biofortis (FRA)	Table of contents	Line 2 Considering the content of the document, it appears that this guidance deals with statistical considerations but also data management, data quality, etc. We could suggest to change the guidance title to "Guidance on study and statistical reporting" for example.	The Terms of Reference as Provided by EFSA states *"The issue of what methodologies should be used for the design, conduct and analysis are outside the scope of this mandate."* . EFSA feels that the title concisely reflects the terms of reference of the mandate and the content of the

No	Contributor	Section	Comments received	EFSA answers
				document.
20	Technical University of Denmark (DNK)	Table of contents	Line 64 It is noted that the guidance in line 162 is expected to have a "glossary of relevant terms". Such a glossary is currently missing.	This comment has been taken into account in revising the "Guidance and template" section.
21	Mondelez International R&D (FRA)	Table of contents	Global comment: Please provide more examples to illustrate and clarify the document. Furthermore, this draft guidance for statistical report recommends providing too many information, with unnecessary precisions (seeing our detailed comments).	The individual detailed comments are addressed below.
22	Mondelez International R&D (FRA)	Table of contents	EFSA validated markers for which there is no quantified biological relevance (glycemic response, satiety, cognitive functions etc...).	This comment is unclear and does not appear to be related to the Table of Contents.
23	Nestlé (CHE)	Background as provided by EFSA	Chapter/Section Background as provided by EFSA Line numbers 141-149 Nestlé Comments Nestlé finds that this guidance is a good forward looking document that will help standardization and transparency. Standardization is needed for statistical reporting of clinical trials used in dossiers submitted to EFSA and Nestlé welcomes this initiative. However Nestlé would like to understand how this guidance will influence dossier writing, since the information and all data required in this guidance are not always available to the applicant. This guidance	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".

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			should not add restriction on how to prepare dossiers for the substantiation of health claims. Typically Nestlé agrees that this guidance suits the reporting of new studies and should be followed for pivotal and proprietary clinical studies submitted in dossier for health claim substantiation; however adherence to this guidance may not be feasible for all already existing historical data and published studies. Indeed for different reasons it may not be possible to go back to the author of historical studies and the related publications may not have all required information: Therefore the application of this guidance should be based on practical, reasonable and proportional grounds. Nestlé would like that harmonization is sought between EFSA and other authorities where dossiers are submitted.	
24	Global Alliance for Probiotics (GAP) (BEL)	Background as provided by EFSA	Line 135 Currently reads ”EFSA work includes…”. This should be “EFSAs work includes…”	Corrected.
25	Technical University of Denmark (DNK)	Background as provided by EFSA	Same as comment 5	Same as comment 5.
26	University of Southampton	Background as provided	Lines 144-5 There is a typo in this sentence, which does not make sense.	The “Background as Provided by EFSA” are quoted

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	(GBR)	by EFSA		verbatim from the mandate and cannot be changed.
27	Mondelez International R&D (FRA)	Terms of reference as provided by EFSA	Lines 154-155 Will the EFSA establish guidance on which statistical methodology is considered as appropriate and how statistical analysis should be performed?	This is outside the scope of this mandate.
28	EuropaBio (BEL)	Terms of reference as provided by EFSA	Line 151-154 It is stated that "guidelines should be developed to best guide … on how to clearly and concisely report statistical methodology …" Given all the requirements listed in the current draft, it will be impossible to have a concise report.	The "Terms of Reference as Provided by EFSA" are quoted verbatim from the mandate and cannot be changed.
29	Mondelez International R&D (FRA)	Terms of reference as provided by EFSA	Lines 166-167 Could the EFSA define what "the SAS Unit" is? Could the EFSA clarify the process of adoption of this guidance document? Does it mean that after the public consultation the guidance document will be reviewed by a working group of EFSA scientific staff and external experts?	The SAS unit was the former "Scientific Assessment Support" but now the mandate is in the remit of Assessment Methodological support Unit (AMU). All public consultation comments are reviewed and discussed by the working group. The guidance and public consultation are also discussed with EFSA's Scientific Committee.
30	Technical University of Denmark (DNK)	Introduction to Guidance	A useful thing would be to identify the most common parts of the guidance that currently aren't followed. If possible, one could review the EFSA reports that have prompted this work, and identify areas that most often lack the precision described in this document. Focus on such areas could be an effective way to minimize	This is outside the scope of this mandate.

No	Contributor	Section	Comments received	EFSA answers
			imprecision. Suggestion: Consider whether the effort of going through present EFSA reports may contribute with sufficient relevant information to justify the work, and if so use them to identify common areas of imprecision.	
31	OCS (NLD)	Introduction to Guidance	Line 176 Please clarify what is meant with "statistical work", only the reporting of statistical results or also the design and/or statistical analysis, or only the tasks related to the primary objectives of the study.	This has been updated to "statistical analysis".
32	OCS (NLD)	Introduction to Guidance	Line 176 Please clarify what is meant with an "appropriately qualified and experienced statistician". For example a degree in statistics and/or registered (bio)statistician in any of the national accreditation systems, like for example the Chartered Statistician from the Royal Statistical Society.	This comment has been taken into account in revising the "Introduction to the Guidance".
33	Technical University of Denmark (DNK)	Introduction to Guidance	Same as comment 5	Same as comment 5
34	EuropaBio (BEL)	Introduction to Guidance	Lines 168-175 Many of the stated requirements appear to come directly from clinical reporting guidelines (as acknowledged in lines 192-194) and are not relevant to the types of studies in the scope of this guidance as listed in lines 170-173. This is reflected not only by the inclusion of certain specific terms (eg line 284 mentions "ethnicity" as a population characteristic)	The diversity of the working group reflects the diversity of EFSA's work and hence this is reflected in the guidance.

No	Contributor	Section	Comments received	EFSA answers
			but also by entire points (eg Line 356 “methods to conceal intervention sequence”). The entire document needs to be overhauled to achieve better alignment with the types of study for which it is intended. Since the study types are diverse, it may not be possible to achieve the goal of encompassing all studies with one template, and there is a risk that the guidance will end up being an unclear mix of requirements and cumbersome to use. Line 169 It would be clearer if this statement said “This guidance is aimed at covering all areas of statistical reporting within EFSA’s remit...”	
35	Nestlé (CHE)	Introduction to Guidance	Chapter/Section Introduction to Guidance Line numbers 180-183 Nestlé Comments Nestlé finds that this guidance is a good forward looking document that will help standardization and transparency. Standardization is needed for statistical reporting of clinical trials used in dossiers submitted to EFSA and Nestlé welcomes this initiative. However Nestlé would like to understand how this guidance will influence dossier writing, since the information and all data required in this guidance are not always available to the applicant. This guidance should not add restriction on how to prepare dossiers for the substantiation of health claims. Typically Nestlé agrees that this guidance suits the reporting of new studies and should be followed for pivotal and proprietary clinical studies submitted in dossier for health claim substantiation; however adherence to this guidance may not be feasible for all already existing historical data and published studies.	Comment 3.

No	Contributor	Section	Comments received	EFSA answers
			Indeed for different reasons it may not be possible to go back to the author of historical studies and the related publications may not have all required information: Therefore the application of this guidance should be based on practical, reasonable and proportional grounds. Nestlé would like that harmonization is sought between EFSA and other authorities where dossiers are submitted.	
36	Food Standards Agency (GBR)	Applicability of Statistical Reporting Guidance	Line 181 The phrase "any analyses" implies that the guidance is all-encompassing. As noted in my general comment on the summary, I do not see how this can be practical (as required by the TOR) when citing multiple published references in an opinion.	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
37	OCS (NLD)	Applicability of Statistical Reporting Guidance	Line 181 "to allow … and validity of any analyses" suggests to refer to defend the methodology used which is outside the scope of this guidance according to line 177-178. Please clarify or rephrase.	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
38	EuropaBio (BEL)	Applicability of Statistical Reporting Guidance	Lines 184-185 It is stated that "Some requirements…are specific to particular situations which will be indicated in the guidance…" However, such indications are rarely provided.	Thank you for your comment.

No	Contributor	Section	Comments received	EFSA answers
39	Technical University of Denmark (DNK)	Applicability of Statistical Reporting Guidance	Same as comment 5	Same as comment 5.
40	Mondelez International R&D (FRA)	Other guidance documents on related topics	This guidance requests are much more demanding than the ICH Guidelines E3, which are currently used for nutrition clinical trials. Could you precise the relevance to provide much more details which may be very difficult to collect / obtain (see our comments in each part) vs the reliability of the data?	This outside the scope of this guidance.
41	Biofortis (FRA)	Other guidance documents on related topics	Lines 210-211 Could EFSA clarify the reference to "internationally accepted terminology"? Do they refer to terminologies such as CDISC, WHO Drug, MedDRA, ...?	This is a quote from EFSA (2009).
42	Technical University of Denmark (DNK)	Other guidance documents on related topics	Same as comment 5	Same as comment 5
43	Mondelez International R&D (FRA)	Guidance and template	Lines 228-235 Will the EFSA update the Scientific and technical guidance for the preparation and presentation of an application for authorization of a health claim regarding statistical reporting?	This outside the scope of this guidance.
44	Global Alliance for Probiotics	Guidance and template	Line 231 Currently reads “In the first case also compliance…”. This should be “In the first case compliance …”	This sentence no longer appears in the revised document.

No	Contributor	Section	Comments received	EFSA answers
	(GAP) (BEL)			
45	Nestlé (CHE)	Guidance and template	Chapter/Section Guidance and template Line numbers 233-240 Nestlé Comments Nestlé would like EFSA to clarify this part, especially what should be understood by "fully reported elsewhere and the guidance does not apply in such cases"? Will a publication in a scientific journal be considered as meeting the criteria of a full report of the statistical analysis? Does this mean that statistical reports of studies supporting an application should not all adopt the format proposed by this guidance? Does this mean that the guidance does not apply to studies for which reports have been issued before the guidance was published? Could EFSA be more specific and give examples where this guidance would not be applicable (i.e. studies for which analyses have been published before the guidance was issued). Should all the studies need to fulfill the criteria set in this guidance, we would like to recommend a proportionate approach on how this guidance applies to studies already published in literature compared to proprietary pivotal studies.	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
46	EuropaBio (BEL)	Guidance and template	Lines 227-235 It is stated that the guidance applies equally to cases where the detailed statistical reporting is in a separate annex or is embedded in the main report. However, if we think of the separate annex as being a document that is written by the statistician then there is a question over whether some of the	This comment has been taken into account in revising the Sections on "Guidance and Template" and "Applicability of Statistical Reporting Guidance" (which has been renamed to "Applicability of This Guidance").

No	Contributor	Section	Comments received	EFSA answers
			requirements are beyond the scope of the statistician's responsibilities and expertise. For example, parts of Sections 4, 5, 6, 8, 10 and 12 would typically not be included in the statistics report. Typically, the statistics report would be a purely technical report and interpretation of the findings and narrative summary would be provided in the main report or reported elsewhere. In this case, it makes more sense to have some requirements addressed within the annex and others addressed within the main report. Some reviewers see the potential for unnecessary duplication here across main report and annex. Please clarify that the requirements listed here apply optionally to either the main report or the annex but both would not be necessary.	
47	EuropaBio (BEL)	1. Title Page	Line 246 The point of including an abstract and key words is unclear. In Lines 125-136, the distinction is made between reports intended for use in a research setting or in a regulatory setting. The requirement for abstract and key words is more appropriate for a research setting than for a regulatory setting. More detailed, and therefore more useful, information is routinely included in the report summary. Possibly the request for a more descriptive title would supersede the need for an abstract. In practice, the set of key words would be unlikely to differ much from one report to another. The suggestion is either to make providing the abstract and key words optional, or to be more specific about what information should be captured.	This comment has been taken into account in revising Section on "Title Page".

No	Contributor	Section	Comments received	EFSA answers
48	Global Alliance for Probiotics (GAP) (BEL)	1. Title Page	Title page beginning line 242 Consider revising to include information pertaining to pre-registration of the study e.g. trial registration. Line 245 The guidance with regard to statistical report title could be more prescriptive. For example change to "Statistical Report Title (covering key information which should include, study design, intervention/exposure or equivalent and objective of study e.g. to evaluate safety)". We suggest that the title should not present results. Line 246 The use of structured abstracts is generally encouraged. We suggest that this should be changed to read "structured abstract and keywords". Line 247 We suggest that a requirement to include any conflict of interests should be added.	This comment has been taken into account in revising Section on "Title Page". The issue of "conflict of interests" is outside the remit of this mandate.
49	Lallemand Health Solutions (CAN)	1. Title Page	Lines 245-250 When the statistical report is a separate document, the title page should also include the name of the main document for which the statistical report is an annex.	This comment has been taken into account in revising Section on "Title Page".
50	Technical University of Denmark (DNK)	1. Title Page	Line 249 It is suggested that the names of persons contributing to the statistical analysis is listed as well. This is in line with the demands in lines 338 (study design) and 357 (randomization and blinding). Furthermore, in particular because the guidance should also be adhered by stakeholders (lines 147-149), it is suggested that the listed people declare their interests, as it may not be obvious from sponsors/funding body.	This comment has been taken into account in revising Section on "Title Page". The issue of "declaration of interests" is outside the remit of this mandate.

No	Contributor	Section	Comments received	EFSA answers
51	Food Standards Agency (GBR)	2. Summary	This implies that the guidance refers only to when a single study is analysed in depth	This comment has been taken into account in revising the Sections on "Guidance and Template" and "Applicability of Statistical Reporting Guidance" (which has been renamed to "Applicability of This Guidance").
52	Mondelez International R&D (FRA)	2. Summary	Lines 256-257 Could the EFSA clarify this sentence?	This comment has been taken into account in revising Section 2.
53	Mondelez International R&D (FRA)	3.2. General objectives	Lines 267- 268 Could the EFSA clarify this sentence?	This is a general sentence that takes into consideration any regulatory requirements.
54	OCS (NLD)	3.3. Specific objectives	Line 277 Unclear what is meant with confidence interval: one-sided vs two-sided or the level of confidence, like the common 95%, or both. Please clarify or rephrase.	This comment has been taken into account in revising Section 3.3.
55	EuropaBio (BEL)	3.3. Specific objectives	Lines 270-275 Specific objectives are sub-divided into three types. The types as stated do not align well with many standard studies in the food and feed safety fields. For example, it is not clear whether a typical biotech compositional study would be regarded as exploratory, estimation or confirmatory. This is important because certain requirements are specific to the type of objective (eg see Section 7, lines 424-432). Lines 278-280 Whilst there is some value in	This comment has been taken into account in revising Section 3.3. The approaches to the assessment of biological relevance are discussed in the Scientific Committees Opinion as referenced in the text.

No	Contributor	Section	Comments received	EFSA answers
			providing an a priori indication of the size of effect that might be considered biologically relevant, assessment of biological relevance is better left as part of the overall risk assessment.	
56	Lallemand Health Solutions (CAN)	3.3. Specific objectives	Lines 276-277 It is not uncommon that a study has multiple endpoints, each with a set of hypotheses to be tested. In such cases, the power of every test would not have been controlled since the experiment would have been initially powered based on only one set of hypotheses, usually the primary endpoint. Hence, reporting post-experiment power estimates for the other hypotheses are non-informative (Hoenig & Heisey, 2001) and should not be encouraged. We recommend that the reference to power of the test be removed. We also recommend that the hypotheses, by endpoint, be listed after the description of the target population not before. Line 277 Specification and justification of the particular confidence interval estimation method to be employed is not a specific objective but a methodology that should be described in the section on statistical analysis (Section 7.2). We recommend moving this sentence to after line 449. Lines 287-288 A short sentence should be added here to indicate that this section pertains mainly to use of existing data and not to experiments for generating new data since much of the detail about experimental studies is required to be provided under Section 5.	The comment on post-hoc power has been taken into account in revising Section 3.3. EFSA feels that it is more natural to specify the question first and the population second. The text on confidence intervals and data sources have been clarified.
57	Technical University of	3.3. Specific	Many of the concepts in the guidance are taken from the area of clinical trials. While this is a relevant	This comment has been taken into account in revising

No	Contributor	Section	Comments received	EFSA answers
	Denmark (DNK)	objectives	application area, it is also an area with very strict defined structures, which for general statistical reporting appear too rigid. The main example on this is that the specific analysis objectives in section 3.3 are separated into only three groups: • Estimation (bullet 2) • Exploratory analysis (bullet 1) • Confirmatory analysis (bullet 3). Furthermore, it is stated (line 552) that "…firm conclusions cannot be drawn based on an exploratory analysis…". While this is in line with usual practice within clinical trials, it seems too narrow for general statistical reporting, even within an organization such as EFSA, in particular when one looks at the specification of the confirmatory analysis in ICH (1998), where it say on a confirmatory trial: "In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always predefined, and is the hypothesis that is subsequently tested when the trial is complete". For the guidance to be of practical use, a person looking for guidance should be able to mirror a sensibly designed statistical analysis in one of the categories. In the present form, this seems to be problematic. For example, for an analysis where an outcome variable is investigated as a function of 3-4 explanatory variables, where the hypothesis is that the explanatory variables describes the outcome, but the exact relation is not clear, it seems unsatisfactory that the result should be classified as analysis from which no firm conclusions	Sections 3.3 and 10.1.

No	Contributor	Section	Comments received	EFSA answers
			can be drawn, as a general rule. In such an analysis, many (statistical) hypotheses may be tested, with corresponding consequences for the relation between outcome and explanatory variables, and it will not be sensible to pre-specify these. It has been noticed that under "Results of statistical analysis" (line 538) it is implicit that analyses can be specified "post-hoc", but it is impossible to decipher such a thing based on a loose sentence in a section on results. It is found that the grouping of objectives is too narrow to cover the general objective of the guidance as formulated in line 169 and the title of the document. Suggestion: It is suggested that the grouping is softened up, either by including a category that may cover the more or less standard statistical analysis with a number of hypothesis tests that cannot sensibly be pre-specified, or otherwise soften up and the definition of confirmatory analysis (along with a rename), so that it is made clear that the category applies to the above situation as well. If EFSA finds that firm conclusions can only be drawn from confirmatory analysis as it is defined within the concept of clinical trials, it is suggested that this is stated explicitly.	
58	Association of the Self-Medication Industry (AESGP) (BEL)	3.3. Specific objectives	Line 276 It is considered appropriate to provide details of power calculations associated with the main objective(s), as per sample size calculation section of the protocol. However, the current wording is possibly suggesting (a) a post-study re-calculation, and/or (b) power calculations for endpoints other than those used to power the study. The companies would not consider this either necessary / appropriate. EFSA is kindly	This comment has been taken into account in revising Section 3.3.

No	Contributor	Section	Comments received	EFSA answers
			requested to clarify the current wording and/or purpose. Line 278 It is stated that "It should be reported whether the existence of a difference or the evaluation of the equivalence is to be assessed". Although this covers the cases of superiority and equivalence / bio-equivalence studies, EFSA may wish to reference non-inferiority studies also. EFSA is kindly requested to clarify this issue. Line 281 It is suggested to use the word "generalisability" rather than "generalisation". Line 284 The term 'ethnicity' is used in the list of examples. Although only an example, it would be considered a clarification if both 'race' and 'ethnicity' were listed here to be clear that these are not generally considered interchangeable. EFSA is kindly requested to clarify this wording.	
59	Nestlé (CHE)	3.3. Specific objectives	Chapter/Section 3.3 Specific objectives Line numbers 276-277 Nestlé Comments Nestlé would like EFSA to comment on this point about the use of exploratory / secondary endpoint in substantiation dossier and to clarify, under which conditions the use of these endpoints could be possible as supportive versus pertinent evidence.	This comment is outside the scope of this guidance.
60	GSK (GBR)	3.3. Specific objectives	• Section 3.3. Specific objectives (line 276): It is considered appropriate to provide details of power calculations associated with the main objective(s), as per sample size calculation section of the protocol. However, the current wording is possibly suggesting (a) a post-study re-calculation, and/or	This comment has been taken into account in revising Section 3.3.

No	Contributor	Section	Comments received	EFSA answers
			(b) power calculations for endpoints other than those used to power the study. GSK CH would not consider either necessary / appropriate. EFSA to clarify wording and/or purpose. • Section 3.3. Specific objectives (line 278): It is stated that "It should be reported whether the existence of a difference or the evaluation of the equivalence is to be assessed". Although this covers the cases of superiority and equivalence / bio-equivalence studies, EFSA may wish to reference non-inferiority studies also. EFSA to clarify.	
61	GSK (GBR)	3.3. Specific objectives	• Section 3.3. Specific objectives (line 281): The word "generalisability" is preferred to "generalisation" • Section 3.3. Specific objectives (line 284): The term 'ethnicity' is used in the list of examples. Although only an example, it would be considered a clarification if both 'race' and 'ethnicity' were listed here to be clear that these are not generally considered interchangeable.	This comment has been taken into account in revising Section 3.3.
62	Technical University of Denmark (DNK)	3.3. Specific objectives	*Same comment repeated in Sections:* • *Reporting of study design* • *Endpoint/objective/outcome* Often in the document, concepts from clinical trials are used directly without reference. The main example of this is the use of the term "endpoint", which is used in a number of situations where the connection to clinical trials is not obvious. In contrast to concept like bias, confounding or macro-editing, it is not possible	The term "endpoint" is also used in toxicology and eco-toxicology. This comment has been taken into account in revising Section 3.3.

No	Contributor	Section	Comments received	EFSA answers
			to do a quick Google search to find out what such a concept means, because the concept is embedded into the general concept of clinical trials. This is undesirable as it is may cause confusion for analysts not familiar with the terminology within clinical trials. While it is acknowledged that clinical trials are a wide application area for statistical analysis, it is not an area where every statistician with their own areas of expertise, not to mention autodidacts, necessarily have their knowledge. It is noted that the guidance in line 162 is expected to have a "glossary of relevant terms". This is currently missing, and inclusion of the term "endpoint" in such a glossary would likely be beneficial. Suggestion: It is suggested that the concept of an "endpoint" is referenced/explained/included in a glossary, and that considerations are made for any similar situations.	
63	OCS (NLD)	3.3. Specific objectives	Line 277 The statement with respect to power seems to be only valid for so called primary endpoints/hypotheses. It is very uncommon to discuss power considerations for secondary and other endpoints/hypotheses. Please clarify what is meant here with 'any' hypothesis.	This comment has been taken into account in revising Section 3.3.
64	Global Alliance for Probiotics	3.3. Specific objectives	Specific objectives beginning line 269 We suggest this should be revised to include a statement of the primary outcomes of the analysis and a list of secondary outcomes. The primary outcome should be	This comment is covered by the bullet point list (i.e. confirmatory versus exploratory).

No	Contributor	Section	Comments received	EFSA answers
	(GAP) (BEL)		the outcome for which the study is powered. Line 279 We suggest that this should be revised to include the possibility of studies aimed at testing the hypothesis of non-inferiority as well equivalence.	
65	Mondelez International R&D (FRA)	3.3. Specific objectives	Lines 276-278 In ICH guidelines, this is only required for the primary objective. Please follow the ICH guidelines.	This guidance covers more than clinical trials.
66	Biofortis (FRA)	3.3. Specific objectives	Lines 270-271 Do "specific objectives" refer to primary and secondary objectives of the studies?	Yes.
67	University of Southampton (GBR)	4. Reporting sources of information	Should it really be necessary always explicitly to state the rationale for use of a specific source of data? For example, if data were generated by a randomised controlled trial, why should it be necessary to justify not using other possible study designs?	The intention is to understand why the chosen source is being used and not the justification of not using other sources.
68	Mondelez International R&D (FRA)	4.1. Existing sources of data	Lines 296-301 Please clarify	It is not clear what needs to be clarified.
69	Food Supplements Europe (BEL)	4.1. Existing sources of data	Line 306 Food Supplements Europe would like to stress that the guidance should not be considered as a way to automatically have full transparency of all data and study methodologies reported. Unpublished data should be able to remain confidential in this is requested by the applicant.	This comment is outside the scope of this guidance.

No	Contributor	Section	Comments received	EFSA answers
70	DSM Nutritional Products (CHE)	4.1. Existing sources of data	Line 306 "Unpublished data should be included in the report." It would be much appreciated if EFSA could keep unpublished data confidential, as far as this is compatible with EFSA's needs and requirements.	This comment is outside the scope of this guidance.
71	EuropaBio (BEL)	5. Reporting of study design	Lines 321-322 For ag-biotech studies, it is common and accepted for multiple transgenic events to be grown together and/or have their samples analyzed together, even though each will be the subject of a separate submission (EFSA Journal 2010; 8(1):1250). Confidentiality issues will arise if protocols/deviations and amendments for these multi-event studies have to be presented.	This comment is outside the scope of this guidance.
72	University of Southampton (GBR)	5. Reporting of study design	Lines 320-321 Listing lots of "not applicables" will make the text rather turgid. Is it really necessary?	In the interest of openness and transparency the reporting should be complete.
73	Global Alliance for Probiotics (GAP) (BEL)	5. Reporting of study design	Line 324 We suggest that not only should omissions in study design be justified but that their impact should also be considered. We suggest a revision to read "…justified and their likely impact considered."	The impact should be reported in Section 10.2.
74	Technical University of Denmark (DNK)	5. Reporting of study design	Same as comment 62	Same as comment 62.

No	Contributor	Section	Comments received	EFSA answers
75	Lallemand Health Solutions (CAN)	5. Reporting of study design	Line 325 Rename Section 5.1 to "Description of the Design of the Experiment/Survey/Study". The requested information includes much more than simply stating the type of design used Line 330 This sentence should be clarified to indicate that either only the biologically relevant effect for the primary endpoint is to be reported or that there should be a table or list of relevant effects for the endpoints of interest in the study. Lines 336-337 These should be combined with the items in line 330. Lines 318-401 This section should be divided into two subsections with some overlap of items. For example, one section should covered all aspects of designed experiments and a separate section should cover all aspects of sample surveys. The designs, implementations, sample size determinations, and inferences (estimation vs hypothesis testing) are usually different for the two types of studies. As a consequence, the current structure given in the document requires separating out information that should be co-incident in a report. Line 340 "Method" should be "Methods". Section 5.2.1 Definitions of experimental/sampling units should be provided as part of the study design, Section 5.1, and should be listed under the bullet on the design of the experiment/study/survey. We recommend that Section 5.2.1 be removed and lines 366-370 be moved to Section 5.1. Lines 371-372 could be moved to Section 7.2. Line 379 Sample size determination for a sample	EFSA intentionally decided not to separate experiment and survey. Methodology is outside the scope of this guidance.

No	Contributor	Section	Comments received	EFSA answers
			survey is usually based on minimizing variance of an estimator or constraining the width of confidence intervals whereas sample size in a planned experiment is based on power of a test which is related to variance and a biologically relevant effect. Hence this bullet could be re-written to clarify that. Section 5.2.3 This section attempts to cover two entirely different aspects of sampling. The first relates to sample surveys and how those surveys (which should have been described in Section 5.1) were actually conducted. For example, a discussion of whether the sampling was probabilistic or non-probabilistic should be included. These items should be retained in this section. The other aspect is the determination of how an experimental design was implemented. It covers sub-sampling and blocking, both of which should have been described as part of the study design in Section 5.1. What was not mentioned but is an important component in some experimental designs is how the subjects were selected for the study. For example, if the subjects are people, it would be important to indicate whether they were randomly selected from the target population or were volunteers. For non-human subjects, such as rats or mice, the source of the animals should be indicated. Lines 383-386 These refer to the sampling design and not to the actual selection of sampling units Lines 390-392 The use of auxiliary information should be given in the study design section or the sample size determination section, not here.	

No	Contributor	Section	Comments received	EFSA answers
			Lines 392-394 The decisions regarding optimizing sample size belongs in the section on sample size determination. Lines 397-399 Lack of independence of sampling or experimental units should have been noted in the study design section not under the sample selection strategy.	
76	GSK (GBR)	5.1. Type of Study Design	• Section 5.1. Type of Study Design (line 338): Although much of this section is as expected, of potential concern is the requirement for detailing of 'persons involved in each phase of the implementation process including providers, data collectors and outcome adjudicators'. It is currently unclear if this may cause issues with regards to privacy laws / personally identifiable information (PII). EFSA to clarify requirements.	The intention is to be as open and transparent. The issue of privacy is important but outside the scope of this guidance.
77	Association of the Self-Medication Industry (AESGP) (BEL)	5.1. Type of Study Design	Line 338 The requirement for detailing of 'persons involved in each phase of the implementation process including providers, data collectors and outcome adjudicators' is seen of a potential concern by some companies. It is currently unclear if this may cause issues with regards to privacy laws / personally identifiable information (PII). EFSA is kindly asked to clarify these requirements.	The intention is to be as open and transparent. The issue of privacy is important but outside the scope of this guidance.
78	Global Alliance for Probiotics (GAP) (BEL)	5.1. Type of Study Design	Type of study design beginning line 325: We suggest that this should be revised to also include a further requirement that information on whether ethical approval for study was gained, should be reported (where ethical approval was required).	This comment has been taken into account in revising Section 5.1.

No	Contributor	Section	Comments received	EFSA answers
			Line 329 We suggest that the description of interventions should include frequency of treatment and any criteria used in assessing whether treatment was given. Line 336 All confounding factors cannot be known and therefore cannot be stated. We suggest this should be changed to read "The primary and secondary endpoints along with the auxiliary and potentially confounding factors (if applicable)".	
79	University of Southampton (GBR)	5.1. Type of Study Design	Lines 336-7 I think it would be better to refer to "potential confounding factors" since it may not be clear whether a factor is a confounder until after the statistical analysis has been carried out. Also, it may be appropriate to mention possible effect modifiers if relevant. Lines 338-9 It might be worth making specific mention of response/participation rates. Line 343-4 I do not think it should be necessary always to justify the choices of cases and controls, but there should be discussion of any implications of the choices for interpretation of the results.	This comment has been taken into account in revising Section 5.1.
80	Mondelez International R&D (FRA)	5.1. Type of Study Design	Lines 326-330 In nutrition, the biological relevance is difficult to quantify in the general population.	This comment is outside the scope of this guidance.
81	Global Alliance for Probiotics	5.1.1. Randomisation and	Type of study design beginning line 350: We recommend more emphasis and detail on reporting blinding. This should include the requirement to report precisely who was blinded (participants, research	This comment has been taken into account in revising Section 5.1.1.

No	Contributor	Section	Comments received	EFSA answers
	(GAP) (BEL)	Blinding	personnel and assessors, as appropriate) and the methods used; guidance on reporting the use of placebos or shams including the requirement that a description of the placebo or sham intervention should be included; and, a statement indicating that statements such as double blind should be avoided as they have no standard meaning (i.e. it is not clear who has been blinded) Line 352 and 355 The use of blocks and stratification is often considered a type of randomisation and therefore the inclusion of both lines may be confusing. We suggest this should be revised accordingly.	
82	OCS (NLD)	5.1.1. Randomisation and Blinding	Line 352 Please explain what is meant here? Central versus local randomization, or dynamic allocation, or also statements like line 355?	This comment has been taken into account in revising Section 5.1.1.
83	Nestlé (CHE)	5.1.1. Randomisation and Blinding	Chapter/Section 5.1.1 Randomisation and blinding Line numbers 349-360 Nestlé Comments In order to gain clarity on the blinding, Nestlé would like EFSA to add the following bullet point: • What measures were taken in order to keep the blind in case of emergency code break (following Serious Adverse Event) or interim analyses. (e.g. type of coding, who is blinded in the study)	This comment has been taken into account in revising Section 5.1.1.
84	OCS (NLD)	5.1.1. Randomisation and	Line 359 Please rephrase 'access to blinding list' to clarify that access to the unblinded randomization list is meant here.	This comment has been taken into account in revising Section 5.1.1.

No	Contributor	Section	Comments received	EFSA answers
		Blinding		
85	Global Alliance for Probiotics (GAP) (BEL)	5.2. Sampling	Line 363 We suggest that the word “according” should be removed as currently it does not make sense.	This comment has been taken into account in revising Section 5.2.
86	University of Southampton (GBR)	5.2. Sampling	Lines 362-4 I do not think that a sample size calculation is essential once a study has been completed. Confidence intervals will give a better indication of statistical power.	This comment has been taken into account in revising Section 5.2.
87	HLS (GBR)	5.2.2. Sample size	P11, line 381 Sample size/power calculations will only be available from a CRO if these have been requested by the client from the CRO at the protocol drafting stage.	This comment is outside the scope of this guidance.
88	Nestlé (CHE)	5.2.2. Sample size	Chapter/Section 5.2.2 Sample size Line numbers 373-381 Nestlé Comments Nestlé would like to have the following clarification added: The level of confidence shall be explicitly stated. e.g. 5% for two sided testing and 2.5% for one sided testing (e.g. ICH E9) further multiplicity will have implication on sample size calculation as well (e.g. multiple groups comparisons in case more than two groups are under investigation, multiple endpoints in case more than one primary outcome is necessary in order to show the objective of the trial. Multiple looks, in case of interim analyses. etc.)	This comment has been taken into account in revising Section 5.2.

No	Contributor	Section	Comments received	EFSA answers
89	Mondelez International R&D (FRA)	5.2.2. Sample size	Lines 374-380 In nutrition, the biological relevance is difficult to quantify in the general population. Could you clarify if the precision of measurements expected here is standard deviation (SD)? Could you clarify if elements such as feasibility, time and budget will be taken into account when reviewing the quality of the analysis?	These comments are outside the scope of this guidance.
90	EuropaBio (BEL)	5.2.2. Sample size	Lines 373-381 This section should mention that, for some types of study, applicants are expected to adhere to minimum sample sizes as specified by EFSA (eg in EFSA Journal 2010; 8(1):1250).	This comment is outside the scope of this guidance.
91	Global Alliance for Probiotics (GAP) (BEL)	5.2.3. Sample selection strategy	"Sample selection strategy" beginning line 382 The draft does not require the reporting of any methods used to adjust for selection issues, such as Heckman selection models. It might be a useful addition to require the reporting of methods used to adjust for selection issues.	Any aspects related to reporting a model used in the analysis is covered in session 7.2.1 of the Guidance irrespective of the purpose of the modelling.
92	Global Alliance for Probiotics (GAP) (BEL)	5.2.3. Sample selection strategy	Lines 384, 385 and 386 This is a repetition of section 5.1.1. We suggest that the primary aim of this section should be to inform on methods used to ensure the representativeness of the study participants (external validity) and not internal validity issues, as these are addressed elsewhere.	This comment has been taken into account in revising Section 5.2.3.
93	Technical University of Denmark (DNK)	5.2.3. Sample selection strategy	Lines 387-389 It is suggested that this sentence is reformulated, so that the contents will be: If the sample selection is not based on a random selection scheme that appropriately reflects the investigation of the study objective (t.ex. representative sampling),	This comment has been taken into account in revising Section 5.2.3.

No	Contributor	Section	Comments received	EFSA answers
			then a justification should be provided. Furthermore, it is suggested that if the sample selection does not appropriately reflect the investigation of the study objective, then the consequences and (if applicable) methods applied to deal with this should be described. The reason for the suggestion is that random sampling is many things, and the fact that the sampling is random does not in itself imply that it is sensible. Random sampling is also a wide concept, which covers t. ex. sampling uniformly at random, stratified sampling to cover t. ex. representative sampling, or targeted sampling where sampling could be uniformly random within clusters of individuals with specific levels of risk. These are all relevant techniques, but each targeted towards specific situations. The deciding factor should be whether the technique reflects what it is meant to investigate, rather than if it is "random".	
94	University of Southampton (GBR)	5.2.3. Sample selection strategy	Lines 388-9 More relevant than comparison with the general population is comparison with the target population about which conclusions are to be drawn. For example, in a study of pesticide sprayers, comparison of the study sample with the wider population of pesticide sprayers would be more relevant than comparison with the general population.	This comment has been taken into account in revising Section 5.2.3.
95	AGES (AUT)	5.2.3. Sample selection strategy	P.12, Line 387 Are there any advices how to deal with risk-based sampling designs? Should just the "deviation" from a random selection and representativeness be stated?	This comment is outside the scope of this mandate.

No	Contributor	Section	Comments received	EFSA answers
96	Mondelez International R&D (FRA)	5.2.3. Sample selection strategy	Lines 383-386 Do you mean that the limitation of budget should be a valid reason for not applying the complete number of subjects as calculated according to the sample size procedure?	This comment has been taken into account in revising Section 5.2.3.
97	Food Standards Agency (GBR)	6. Reporting data quality	This again implies when assessing a single study rather than multiple studies. Such mixed messages are throughout the guidance	This comment has been taken into account in revising Section on "Applicability of Statistical Reporting Guidance" which has been renamed to "Applicability of This Guidance".
98	Biofortis (FRA)	6. Reporting data quality	Line 402 In order not to make the report too bulky, we suggest that these data could be made available on request for review in electronic format.	EFSA would like to avoid having to go back to authors for information where possible including on the issue of quality.
99	Lallemand Health Solutions (CAN)	6.1. Data collection quality assurance	Line 416 Imputation of missing data is not quality assurance. This sentence should be changed to "If imputation for missing data was employed, then the actions taken to ensure that bias was not introduced and that variance was not compromised should be described".	This comment has been taken into account in revising Section 6.1.
100	OCS (NLD)	6.1. Data collection quality assurance	Line 416 Please delete this sentence here: "methodology used to impute missing data" is part of statistical analysis (see line 440) and out of scope of data collection: data collection should aim to minimize missing data, not to impute.	This comment has been taken into account in revising Section 6.1.

No	Contributor	Section	Comments received	EFSA answers
101	Global Alliance for Probiotics (GAP) (BEL)	6.1. Data collection quality assurance	Line 416 We suggest adding the requirement for a description of methods which have been adopted to minimise the amount of missing data. Furthermore the reporting of methods to deal with missing data currently appears in a number of sections (6.1 or 7.1 (line 440)). This is not necessary and may lead to confusion. Line 422 Reference to weighting by methodological quality is repeatedly referenced in the guidance. In our experience this is rarely done in practice and is generally discouraged as it is has been demonstrated to produce inconsistent and unreliable results.(4-6) While the aim of the draft guidance is on reporting rather than methods used and therefore the guidance should not preclude this form of analysis, the repeated references to this form of analysis may be interpreted as implicit approval for weighting by methodological quality. We would recommend strongly that all references to this practice should be removed from the guidance, or if retained, it should be made clear that this practice is not standard and needs to be justified in detail.	This comment has been taken into account in revising Section 6.1.
102	University of Southampton (GBR)	6.1. Data collection quality assurance	Lines 421-2. This should not be taken to imply that studies should necessarily be scored for quality. Such scoring systems are widely used, and have the advantage of making assessment more reproducible within and between reviewers. However, this may be at the cost of a loss in validity. For example, if an epidemiological study found a positive association with a risk factor, it would be inappropriate to give the finding less weight because the study was liable to	Methodology is outside the scope of this guidance.

No	Contributor	Section	Comments received	EFSA answers
			important bias, if in fact the effect of such bias would be to cause underestimation of risk.	
103	Nestlé (CHE)	6.1. Data collection quality assurance	Chapter/Section 6.1. Data collection quality assurance Line numbers 411, 414, 417 Nestlé Comments Nestlé would like EFSA to clarify these points. Would internal processes such as initiation visits, data validation plan and instrument calibration logs be considered adequate?	Guidance is intended to cover all aspects of quality assurance in data collection. Examples provided are quite specific to clinical trials and hence outside the scope of this guidance.
104	Technical University of Denmark (DNK)	6.1. Data collection quality assurance	*Same comment repeated in Section:* • *Statistical analysis* Line 416 It is suggested that imputation is removed from this list and considered in section 7.2, where it is already mentioned under pin no. 9. The reason is to dissociate imputation from data. Imputation is a technique employed to allow models to make the most of data, but imputed values are not data themselves, and the distinction should be made clear.	This comment has been taken into account in revising Section 6.1.
105	EuropaBio (BEL)	6.1. Data collection quality assurance	Lines 408-417 For studies conducted under GLP, this information is kept within the study records and adherence can be assumed; there should be no need for further reassurance or description of this information in the report other than a GLP Compliance Statement and/or Quality Assurance Statement. Line 416 In general, missing data should not be imputed. Lines 418-422 The wording of this paragraph is difficult to understand; some re-wording is called for.	GLP does not guarantee good statistical reporting or practice.

No	Contributor	Section	Comments received	EFSA answers
106	Mondelez International R&D (FRA)	6.1. Data collection quality assurance	Line 411 This kind of information is never required. To our knowledge, only the investigator curriculum vitae and competencies are usually required. Line 417 Could you provide some example?	Training is commonly done and is part of the quality assurance.
107	University of Southampton (GBR)	6.1. Data collection quality assurance	Lines 414-5 A detailed listing of all checks could be rather long. Is it always essential? Usually it would be sufficient to know broadly what sorts of checks had been carried out to look for errors.	All lists of checks are relevant and should be provided.
108	University of Southampton (GBR)	7. Reporting the Methods of Analysis	Lines 424-427 Even in a confirmatory study, it may not be possible to specify in advance the exact method of analysis. For example, the cut-points used to partition a variable might depend on its distribution in the study sample.	EFSA accept it is not possible to plan all the details of the analysis in advance. We are asking for reporting simply plan and deviations from it.
109	Lallemand Health Solutions (CAN)	7. Reporting the Methods of Analysis	Section 7.1 Presumably this section refers to activities and actions related to constructing data that would be used in the statistical analyses and the descriptive summaries described in sections 7.2 and 9.1.1. As such, it would be advantageous to add a sentence to that effect to clarify that this section is not referring to the calculations used in the descriptive statistics but instead focuses on the construction of derived statistics such as is done when converting a continuous variable to ordinal categories before analysis. If it is not intended for that purpose, then it is somewhat redundant since each bullet is described elsewhere in the other sections. Lines 436-437 Transformations are used in two ways	This comment has been taken into account in revising Section 7.

No	Contributor	Section	Comments received	EFSA answers
			in analyses. The first is when data are usually reported on a transformed scale (e.g. pH units, geometric means, or similar) and the second, is when transformations are applied in order to satisfy the assumptions of a statistical model, e.g. using a square root transformation to achieve homogeneous variance and approximate normality. We recommend that this bullet be used to indicate the first circumstance and that a bullet be added to Section 7.2 indicating that transformations for analytical purposes and to meet assumptions be described. Lines 440-441 It is unclear why treatment of missing or censored data and outliers are listed here when they are more fully treated in lines 468-471. We recommend that lines 440-441 either be removed from this section or have qualifiers that distinguish them from the reporting requirements in lines 468-471. Lines 470-471 We recommend that the implications and justification of imputation also be included in this bullet. For example use of the Last One Carried Forward method increases the degrees of freedom for the error sums of square and so makes hypotheses tests more liberal than they should be. Lines 475-476 The statement "… and justification of … methods to handle multiplicity …" should be modified. As it is written the implication is that handling multiplicity must be justified whereas the reality is that it is justified by many years of statistical theory. Instead, the statement should read that if adjusting for multiplicity is warranted but not performed, then its non-use should be justified.	

No	Contributor	Section	Comments received	EFSA answers
			Line 478 Again, the methods used for testing and checking model assumptions are standard statistical practice and so should not require justification. The sentence should be modified to indicate that justification is required if standard statistical methods are not used to check model assumptions. Lines 483-484 Remove "and justification"	
110	EuropaBio (BEL)	7. Reporting the Methods of Analysis	Line 424 The statement "When analysing confirmatory studies and estimation…" is not right grammatically.	This comment has been taken into account in revising Section 7.
111	Technical University of Denmark (DNK)	7. Reporting the Methods of Analysis	*Same comment repeated in Sections:* • *Statistical analysis* • *Results of statistical analysis* • *Reporting Uncertainty* A standard feature that is often overlooked is the model justification. In our experience, it is one of the most common causes for erroneous analysis. While the concept is mentioned in section 7.2, pin no. 6, in section 9.1.2 and to some degree in section 10.2, the concept seems underplayed and open to too much interpretation, in particular when the general paras in the introduction, lines 177-178, that "…The issue of what methodologies should be used for the design, conduct and analysis are outside the scope of this mandate …", while obviously sensible, opens up for undesirable interpretations on model justification. While it is clear that there is no reason to limit the	This comment has been taken into account in revising Section 7.

No	Contributor	Section	Comments received	EFSA answers
			choice of analysis method, design etc., it should not be so that the model justification is something where the choice of method is too open to what might end up in superficial techniques. Even for experienced and qualified statisticians, it is likely that an increased focus on model justification will have an effect. Furthermore, even if correct model justification is carried out, it is found that the risk of neglecting inclusion in reports is too big with the current formulations, as report writers and analysts may have different views on the importance. Suggestion: It is suggested that model justification is dealt with in a separate subsection of section 7, along with t. ex. data processing.	
112	Mondelez International R&D (FRA)	7.1. Data processing	Line 440 What means “censored data”?	This comment is outside the scope of the guidance.
113	Global Alliance for Probiotics (GAP) (BEL)	7.1. Data processing	Line 442 Methods of weighting are already required in section 6.1. We suggest that this should be removed from this section to avoid repetition.	Weighting in the two sections covers different aspects.
114	OCS (NLD)	7.2. Statistical analysis	Line 463 Please clarify ‘If applicable intermediate model results should be shown for model building’. Does this mean that all model outputs should be presented or presenting criteria for choosing the model would be enough?	This has been deleted now.

No	Contributor	Section	Comments received	EFSA answers
115	Technical University of Denmark (DNK)	7.2. Statistical analysis	Same as comment 111.	Same as comment 111.
116	Technical University of Denmark (DNK)	7.2. Statistical analysis	Same as comment 104	Same as comment 104.
117	University of Southampton (GBR)	7.2. Statistical analysis	Lines 45--2 The choice of probability levels for interval estimation is somewhat arbitrary, and should not require justification as long as it is clear what probability level was used. When reporting the results of hypothesis testing, it is more informative to give exact p-values than comparison with a specified level of probability. However, it is helpful to justify the criteria that are used for inclusion of covariates in statistical models.	This comment has been taken into account in revising Section 7.2.
118	Mondelez International R&D (FRA)	7.2. Statistical analysis	Lines 448-449 Could you clarify? Lines 453-454 The main interest is to justify the selected model. It is not relevant to consider all alternative models for which the relevance may be difficult to assess. Line 460 Usually softwares do not provide this kind of information and it appears not appropriate to provide this information. Line 472 Usually methods are published. Could you specify if a reference would be sufficient?	This comment has been taken into account in revising Section 7.2. Model specification is not a software issue. A reference would be sufficient provided that a description of the method is given in the report too.

No	Contributor	Section	Comments received	EFSA answers
119	Global Alliance for Probiotics (GAP) (BEL)	7.2. Statistical analysis	Line 462 We suggest that this be removed as fixed effect and random effects can mean different things in different contexts (see fixed effects model Wooldridge et al (7) and fixed effects meta-analysis Higgins et al (8)). This issue is also likely to be covered by the general requirement to detail the methods of analysis in line 457. Line 464 to 466 The requirement that all assumptions be specified and justified seems unreasonably onerous and indeed may not be possible where those assumptions are not testable. We suggest that this is revised to require the reporting of key assumptions and justification of these assumptions. Line 467 to 469 The requirement to report the choice of data selected would likely cover any exclusions and so make line 468 and 469 superfluous. Line 470, 471 472 This appears to be repetition as it is a requirement that these be reported elsewhere (see line 416, 420-422 and 440-442), so we suggest that it is removed.	These comments have been taken into account in revising Sections 7.1 and 7.2.
120	EuropaBio (BEL)	7.2. Statistical analysis	Line 470 In general, missing data should not be imputed.	This comment has been taken into account in revising Sections 7.1 and 7.2.
121	HLS (GBR)	7.3. Software	P14, line 489 Analysis may be performed by software developed in-house. Code for an entire application cannot be readily provided.	This comment has been taken into account in revising Section 7.3.

No	Contributor	Section	Comments received	EFSA answers
122	EuropaBio (BEL)	7.3. Software	Lines 492-493 The wording here implies that provision of programs, logs and outputs in electronic format is not a default requirement. If so, please state this explicitly. Lines 493-494 Inclusion of program name, date and time run on each table, graph and listing seems excessive and unnecessary, especially for tables and graphs included in the main report. For most ag-oriented studies, all analyses will have been run as part of the same program, at the same time.	This comment has been taken into account in revising Section 7.3.
123	Technical University of Denmark (DNK)	7.3. Software	Line 494 It is suggested that the demand for accompanying graphs, tables etc. with data and time for when they were created is removed. It seems to be redundant information which will cause irritation and lessen the overview, while contributing with little information if the software, version number and operating system is already supplied.	This comment has been taken into account in revising Section 7.3.
124	Association of the Self-Medication Industry (AESGP) (BEL)	7.3. Software	Line 493 Currently, the companies practice is to date-stamps all statistical output. However, time-stamping is not currently performed. EFSA is kindly requested to confirm how the absence of time-stamping may affect acceptance/rejection of a submission.	This comment has been taken into account in revising Section 7.3.
125	GSK (GBR)	7.3. Software	• Section 7.3 Software (line 493): Currently, GSK CH date-stamps all statistical output. However, time-stamping is not currently performed. Is time stamping a requirement EFSA to confirm how the absence of time-stamping	This comment has been taken into account in revising Section 7.3.

No	Contributor	Section	Comments received	EFSA answers
			may affect acceptance/rejection of a submission.	
126	Technical University of Denmark (DNK)	7.3. Software	Lines 489-491 It is suggested that exceptions are mentioned for products which are/are being commercialized, with a corresponding need for discretion, and that this situation should be handled according to the procedure in lines 486-488.	This comment has been taken into account in revising Section 7.3.
127	Nestlé (CHE)	7.3. Software	Chapter/Section 7.3. Software Line numbers 492-493 Nestlé Comments Nestlé would recommend the use of adequate software for statistical analysis (the two main being R and SAS) providing reproducible calculation for the outputs and availability of logs. These softwares should ease the internal peer review of data and allow double programming of primary outcome. Typically the format for the data set should be in the CDISC format.	This is outside the scope of this guidance.
128	AGES (AUT)	7.3. Software	P.14, line 492 Do programs, log and output have only to be available ON REQUEST by EFSA for review?	This comment has been taken into account in revising Section 7.3.
129	Nestlé (CHE)	8. Deviation from the protocol and/or analysis plan	Chapter/Section 8. Deviation from the protocol and/or analysis plan Line numbers 495-497 Nestlé Comments Nestlé would like EFSA to clarify if they would like to receive logs collected during clinical studies containing all the protocol deviations and as well analyses of the intention to treat (ITT) vs per protocol (PP) study population.	This comment has been taken into account in revising Section 8.

No	Contributor	Section	Comments received	EFSA answers
130	EuropaBio (BEL)	8. Deviation from the protocol and/or analysis plan	Lines 495-497 It is unclear precisely what the term "protocol" refers to here, and in particular whether it refers to a document that relates just to the statistical analysis or to a document that is far more wide-ranging. Please clarify. Typically, the statistical analysis of study data is part of a (GLP) study and not a study in itself, in which case any documentation on planned or unplanned changes to the study protocol is presented in the GLP study report. In addition, according to the OECD GLP principles it is not required to include study protocols, amendments and deviations in a GLP study report. However, in some cases the statistical analysis would be regarded as a study in itself.	This comment has been taken into account in revising Section 8.
131	OCS (NLD)	9. Reporting the Results	Line 501/02 Presenting results in the transformed as well as in the original scale is not sensible and may be misleading. For example, a simple straightforward model without interaction terms on the log-scale, will imply an interaction term on the original scale. An explanation of the reason to transform should be given, not the results on both scales. What if a certain transformation is already decided in a SAP? Do we still need to conduct analysis on the original scale which actually means not much for us scientifically?	This comment has been taken into account in revising Section 9.
132	Biofortis (FRA)	9. Reporting the Results	Line 499 Could EFSA clarify the reference to "modelling outputs"? Do they mean the exhaustive statistical outputs (i.e. for instance complete outputs from the different SAS Procedures that produce statistical results) or summary of statistical outputs? We would recommend to present summary of	This comment has been taken into account in revising Section 9.

No	Contributor	Section	Comments received	EFSA answers
			statistical modelling outputs, but to make exhaustive statistical modelling outputs available on request for review. Lines 500-502 Could you please confirm that EFSA require to present both raw data and transformed data for descriptive statistics only, and not for parameter estimates from the statistical modeling?	
133	EuropaBio (BEL)	9. Reporting the Results	Lines 500-502 It is felt that, in cases where a transformation has been applied, presentation of results on both the transformed scale and the original scale should be optional rather than mandatory.	This comment has been taken into account in revising Section 9.
134	Lallemand Health Solutions (CAN)	9. Reporting the Results	Lines 512-513 This sentence should indicate that the summary statistics should be provided for each treatment level or sub-group in the population and not for all groups or levels combined. Lines 519-520 These presentations may not be of any use – many planned experiments have relatively small sample sizes within each level of the treatment structure and so these would be non-informative. We recommend that this be removed and that instead, a change to line 533 to indicate distributional review should be added Line 533 Add "including graphical displays of the residuals and of any plots (such as Q-Q plots) used in determining the distribution of the data"	This comment has been taken into account in revising Section 9.
135	AGES (AUT)	9. Reporting the Results	P.15, line 500 It is required to present results for both transformed values and in the original measurement units. But that's not always that easy, e.g. the expected	This comment has been taken into account in revising Section 9.

No	Contributor	Section	Comments received	EFSA answers
			value E(Y) is not the same as exp(E(log Y)). How should this "back-transformation" to the original scale be performed? Are there any "guidelines", e.g. to use Taylor series for approximation?	
136	Global Alliance for Probiotics (GAP) (BEL)	9. Reporting the Results	Line 500-502 The justification for this is unclear, especially when the transformation is reversible by the reader and this seems to be an onerous requirement that is of minimal benefit. We suggest that this be removed.	This comment has been taken into account in revising Section 9.
137	EuropaBio (BEL)	9.1. Endpoint/objective/outcome	Lines 504-505 The proposal for sub-section structure (i.e. by endpoint, objective or outcome) is unclear. Specifically, it is unclear whether all three of the proposed structures are acceptable alternatives and whether the applicant is free to choose whichever structure they prefer. Often, a study will only have one objective, relating to all endpoints. Creating a separate sub-section for each endpoint does not seem sensible.	This comment has been taken into account in revising Section 9.
138	Technical University of Denmark (DNK)	9.1. Endpoint/objective/outcome	Same as comment 62	Same as comment 62
139	Biofortis (FRA)	9.1.1. Descriptive statistics	Lines 507-508 In addition to comment on summary, we would suggest to present all data collected which match with study objectives, as some data may be collected but not yet recorded in the database, for further exploratory analysis for example.The sentence	This comment has been taken into account in revising Section 9.

No	Contributor	Section	Comments received	EFSA answers
			should therefore be the following one: "Descriptive statistics should be presented for all data considered in an analysis, whether used in the final analysis or not." Lines 518-520 We could suggest here not to give a detailed list of descriptive statistic measures to absolutely report, but only examples. In fact, we consider that normality distribution should not always be checked (by statistical tests or graphical representations), depending of the work hypotheses. In addition, in our view, we consider that means and standard deviations can be reported even in case of non normality.	
140	University of Southampton (GBR)	9.1.1. Descriptive statistics	Line 515 I am not sure that it adds much value always to give all three of percentage, numerator and denominator, and it can make tables of results rather cluttered. Two of the three will often be sufficient. Line 517 Some measure of central tendency and dispersion is needed, but is it necessary to be quite so prescriptive?	First comment, typos can be spotted and QC (e.g. across results). Some interpret percentages better than numbers and vice versa. The second comment has been taken into account in revising Section 9.
141	EuropaBio (BEL)	9.1.1. Descriptive statistics	Lines 517-520 Presentation of median, lower quartile and upper quartile makes little sense in cases where the number of replicates per entry per location is low, as is common for ag-oriented studies. It is also additional to what is stated in the current EFSA (2010) guidance for food and feed studies. Moreover, for data where the data distribution is approximately normal, mean and standard deviation are the sufficient descriptive statistics. Similarly, a graphical presentation of "the distribution" is not really appropriate for data arising from designed experiments	This comment has been taken into account in revising Section 9.

No	Contributor	Section	Comments received	EFSA answers
			involving multiple factors and/or multiple hierarchies (eg multiple replicates nested within multiple locations for each of multiple treatments) as the data are not samples from a single population but instead come from multiple populations with potentially different means (and possibly different variances).	
142	OCS (NLD)	9.1.1. Descriptive statistics	Line 519 Please clarify that the assumption on normality is that the error terms in the statistical model need to be normally distributed, not the raw data itself.	Methodology is outside the scope of this guidance. This comment has been taken into account in revising Section 9.
143	Global Alliance for Probiotics (GAP) (BEL)	9.1.1. Descriptive statistics	Line 515 We suggest that "proportion" rather than "percentage" is the more appropriate term. Line 519 We suggest that this should reference to parameters that are normally distributed post transformation i.e. log normal. Line 521 Sources of heterogeneity can only be described as potential if there is evidence to support a particular modifying effect. We suggest this should be revised to read: "In case of systematic review any potential sources of heterogeneity should be described at least in a narrative…"	This comment has been taken into account in revising Section 9.
144	AGES (AUT)	9.1.1. Descriptive statistics	P.15, line 515 What is meant by presenting the percentages with both the numerator and the denominator(s)? Should it be reported as a fraction rather than as percentage?	This comment has been taken into account in revising Section 9.
145	Technical University of Denmark	9.1.2. Results of statistical	Same as comment 111	Same as comment 111.

No	Contributor	Section	Comments received	EFSA answers
	(DNK)	analysis		
146	Mondelez International R&D (FRA)	9.1.2. Results of statistical analysis	Lines 528-538 Could you clarify what time of results do you expect on this part? The validation of the model is based on all the previous explanations provided in Sections 5 to 7. What do you expect as additional information?	This section relates to the reporting of the results.
147	Technical University of Denmark (DNK)	9.1.2. Results of statistical analysis	Line 525 It is suggested that not only point estimates and intervals, but also p-values are presented, as a measure of the degree of statistical significance, which may not always be apparent from the intervals.	P-values can still be reported (see EFSA Scientific Committee (SC), 2011. Statistical Significance and Biological Relevance. EFSA Journal 2011;9(9):2372, 17 pp. doi:10.2903/j.efsa.2011.2372).
148	Global Alliance for Probiotics (GAP) (BEL)	9.1.2. Results of statistical analysis	Line 526 and 527 The draft guidance requires: "Where the analysis provides full distribution for estimators they should be provided (e.g. Bayesian method, bootstraps)." The meaning of "provide the full distribution" is unclear. We suggest that EFSA should provide further details to clarify this.	This comment has been taken into account in revising Section 9.1.2.
149	EuropaBio (BEL)	9.1.2. Results of statistical analysis	Line 532 In general, missing data should not be imputed.	This comment has been taken into account in revising Section 9.1.2.
150	Global Alliance for Probiotics (GAP) (BEL)	9.1.3. Graphical summaries	Section 9.1.3 beginning line 539 In our experience clarity in graphs can be lost where measures of dispersion are added. We suggest adding a note indicating that these should only be presented where they can be read clearly.	This is addressed in the first sentence of this section.

No	Contributor	Section	Comments received	EFSA answers
151	Biofortis (FRA)	9.1.3. Graphical summaries	Line 539 Which graphs are the more relevant according to EFSA? Graphs based on raw data ("descriptive graphs") or based on data from parameter estimates from the statistical modeling (Lsmeans for instance -> "inferential graphs")?	Methodology is outside the scope of this guidance.
152	Lallemand Health Solutions (CAN)	10. Reporting the interpretation of the results	Line 565-566 In addition to discussing the extent to which assumptions are valid it may also be helpful to require discussion of how deviations from these assumptions are likely to impact on the results. Deviations from normality have, for example, been demonstrated to often have minimal impact on estimates.	This comment has been taken into account in revising Section 10.
153	Global Alliance for Probiotics (GAP) (BEL)	10.1. Reporting results and their interpretation	Line 555-557 Heterogeneity can occur in meta-analysis for a range of reasons, e.g. differences in setting or participant characteristics. These should be discussed in addition to any difference in methodological quality. Furthermore, weighting cannot be carried in a non-statistical pooling of the data, so we suggest that reference to this should be removed.	This comment has been taken into account in revising Section 10.
154	Mondelez International R&D (FRA)	10.1. Reporting results and their interpretation	Line 553 In nutrition, the biological relevance is difficult to quantify in the general population.	This comment is outside the scope of this guidance.
155	Nestlé (CHE)	10.1. Reporting	Chapter/Section 10.1. Reporting results and their interpretation	This comment has been taken into account in revising Section 10.1.

No	Contributor	Section	Comments received	EFSA answers
		results and their interpretation	Line numbers 549-554 Nestlé Comments Could EFSA clarify whether exploratory and secondary endpoints should be understood in the same way? Could EFSA indicate whether secondary endpoints as well as exploratory analysis could nevertheless be used as "supportive evidence" as opposed to pertinent (i.e. studies using the food/constituent and with appropriate outcome measures in a group that is representative of the target group for the claim)	
156	Technical University of Denmark (DNK)	10.2. Reporting Uncertainty	Same as comment 111	Same as comment 111.
157	Global Alliance for Probiotics (GAP) (BEL)	10.2. Reporting Uncertainty	Line 565 and 566 In addition to discussing the extent to which assumptions are valid it may also be helpful to require discussion of how deviations from these assumptions are likely to impact on the results. Deviations from normality have, for example, been demonstrated to often have minimal impact on estimates.	This comment has been taken into account in revising Section 10.2.
158	Technical University of Denmark (DNK)	10.2. Reporting Uncertainty	Same as comment 5	Same as comment 5.
159	Biofortis	10.2.	Line 558 Could EFSA clarify the reference to	Uncertainty goes beyond confounding factors and

No	Contributor	Section	Comments received	EFSA answers
	(FRA)	Reporting Uncertainty	"uncertainty"? Do they mean for instance the impact of confounding factors?	we refer you to the reference EFSA (2009) for further information.
160	University of Southampton (GBR)	10.2. Reporting Uncertainty	Line 567 It would be better to say "potential magnitude". If the exact magnitude were known, there would be no uncertainty.	This comment has been taken into account in revising Section 10.2.
161	Mondelez International R&D (FRA)	10.2. Reporting Uncertainty	Lines 559- 561 The uncertainty on the main criteria is fully relevant. However uncertainties on each outcome may be too much information.	EFSA does not agree with this comment.
162	Technical University of Denmark (DNK)	10.2. Reporting Uncertainty	Lines 565-571 It is suggested that a reflection on what is reported here is also provided, ie. a listing of weaknesses of the analysis and possibly particular strengths. The reason is that the reader may not be able to deduce the impact of model violations, lack of representativity etc, and consequences of the extent to which assumptions on these are valid.	The intention of describing the uncertainty to enable the readers to judge the validity and limitation of the reported analysis in the context of the objectives.
163	Lallemand Health Solutions (CAN)	11. Detailed Statistical outputs	Section 11 This entire section is already covered in Section 9. If it refers to the detailed output from each analysis, then that is covered under Section 12. Hence, it appears to be repetitive with other sections.	This comment has been taken into account in revising Section 11.
164	Global Alliance for Probiotics (GAP) (BEL)	11. Detailed Statistical outputs	Line 573 and 574 EFSA should provide further guidance on what constitutes “essential” and “important”. We suggest revising the text to read: “The essential/ important results should be presented in summary form in the body of the report and should	This comment has been taken into account in revising Section 11.

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			reflect the primary objectives of the report and not the statistical significance of parameters."	
165	Biofortis (FRA)	11.1. Tables	Line 577 Could EFSA clarify the reference to "modelling outputs"? Do they mean the exhaustive statistical outputs (i.e. for instance complete outputs from the different SAS Procedures that produce statistical results) or summary of statistical outputs? We would recommend to present summary of statistical modelling outputs, but to make exhaustive statistical modelling outputs available on request for review.	This comment has been taken into account in revising Section 11. EFSA intends to be open and transparent in its report by providing comprehensive outputs. Further EFSA would like to avoid having to go back to authors for the results.
166	EuropaBio (BEL)	11.2. Graphs	It is not clear whether the requirement is to provide a graphical summary, as well as a tabular summary, for every endpoint. To have to present both automatically will likely result in unnecessary duplication in many cases.	This comment has been taken into account in revising Section 11.
167	EuropaBio (BEL)	11.3. Listings	Line 582 Provision of a data listing in hard copy form seems unnecessary given that applicants are required to provide the data in electronic format. A full data listing could run to a great many pages.	Section 11.3 was removed.
168	University of Southampton (GBR)	11.3. Listings	Line 582 "is referenced" should be "are referenced".	Section 11.3 was removed.
169	EuropaBio (BEL)	12.1. Protocol and protocol	Line 587 It is unclear precisely what the term "protocol" refers to here, and in particular whether it refers to a document that relates just to the statistical analysis or to a document that is far more wide-	This comment has been taken into account in revising Section 12.1. The guidance makes a distinction between a protocol

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		amendments	ranging. Please clarify. As protocol amendments are required, please clarify whether protocol deviations are also required? Typically, the statistical analysis of study data is part of a (GLP) study and not a study in itself, in which case any documentation on planned or unplanned changes to the study protocol is presented in the GLP study report. In addition, according to the OECD GLP principles it is not required to include study protocols, amendments and deviations in a GLP study report. However, in some cases the statistical analysis would be regarded as a study in itself. For ag-biotech studies, it is common and accepted for multiple transgenic events to be grown together and/or have their samples analyzed together, even though each will be the subject of a separate submission (EFSA Journal 2010; 8(1):1250). Confidentiality issues will arise if protocols/deviations and amendments for these multi-event studies have to be presented.	(Section 12.1) and a statistical analysis plan (Section 12.3). EFSA remit covers GLP and non-GLP studies.
170	Mondelez International R&D (FRA)	12.5. Raw data	Lines 592-593 Databases are confidential information and sharing this information should be required only on specific cases and under specific confidential agreement.	This comment is outside the scope of this mandate.
171	EuropaBio (BEL)	12.5. Raw data	Lines 593-595 The wording here implies that provision of a data dictionary is mandatory. However, for most ag-oriented studies, variables are either self-explanatory or else defined in the report, in which case there should be no need for a data dictionary. The provision of a data dictionary should therefore be optional.	The intention of requiring a data dictionary is to remove the subjectivity of what "self-explanatory" means to each individual.

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172	Nestlé (CHE)	12.5. Raw data	Chapter/Section 12.5. Raw data Line numbers 591-595 Nestlé Comments Nestlé welcomes the idea to provide raw data in electronic format. Here we would recommend using already accepted standard such as CDISC. Nestlé would like as well to clarify if EFSA would like to have the raw data or source data from clinical studies.	The format of the delivery of the raw data is outside the scope of this mandate. EFSA is addressing this issue via other projects.
173	EuropaBio (BEL)	12.7. Unpublished references	Line 597 Please clarify whether the intention here is to include the full text for unpublished references. There should also be a section in which published references are listed.	Text updated (see Section 3.1). Sections 12.6 and 12.7 removed. Section added for references.
174	Association of the Self-Medication Industry (AESGP) (BEL)	12.8. Quality assurance procedures	Line 599 Some general principles regarding QC/QA measures will be outlined within the protocol. However, the companies adhere to a detailed and specific set of internally agreed processes and procedures which meet industry standards with regards to the collection, manipulation and statistical reporting of data. QC programs and outputs can be quite lengthy and not necessarily aesthetically pleasing. EFSA is kindly requested to clarify what is considered important so that the companies can assure that they have and follow adequate processes and procedures or physical evidence that QC has been performed.	The current wording gives the flexibility to the authors to provide the level of details necessary to assure the reader that there was adequate QC/QA.
175	Biofortis (FRA)	12.8. Quality assurance procedures	Line 598 We suggest that these data could be made available on request for review.	EFSA intends to be open and transparent in its report by providing comprehensive outputs. Further EFSA would like to avoid having to go back to authors for the results.

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176	GSK (GBR)	12.8. Quality assurance procedures	Section 12.8. Quality assurance procedures (599): Some general principles regarding QC/QA measures will be outlined within the protocol. However, GSK CH adheres to a detailed and specific set of internally agreed processes and procedures which meet industry standards with regards to the collection, manipulation and statistical reporting of data. QC programs and outputs can be quite lengthy and not necessarily aesthetically pleasing. EFSA to clarify what is considered important (assurance that we have and follow adequate processes and procedures or physical evidence that QC has been performed).	The current wording gives the flexibility to the authors to provide the level of details necessary to assure the reader that there was adequate QC/QA.
177	Global Alliance for Probiotics (GAP) (BEL)	12.8. Quality assurance procedures	Line 600 It is not clear what the abbreviation "QC" means. This should be written in full. Line 600-602 The sentence beginning "These can include data…" does not make sense. What are we attempting to ensure by quality control measures.	This comment has been taken into account in revising Section 12.8.
178	EuropaBio (BEL)	12.8. Quality assurance procedures	Lines 598-603 These are available in GLP study records and SOPs.	EFSA remit covers GLP and non-GLP studies.